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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/597,753	09/20/2006	Rene Hersperger	33647-US-PCT	5799

75074 7590 10/20/2009

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EXAMINER	
MABRY, JOHN	

ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
10/20/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/597,753	HERSPERGER ET AL.	
	Examiner	Art Unit	
	JOHN MABRY	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 0209*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *6 and 9-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/06; 11/01/06; 8/7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner's Response

Applicant's response on July 8, 2009 filed in response to the Election/Restriction dated April 10, 2009 has been received and duly noted. The Examiner acknowledges Applicants' election of Group II without traverse.

Thus, the restriction requirement is deemed proper and **FINAL**.

In view of this response, the status of the rejections/objections of record is as follows:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "linker" in claim 1 is a relative term which renders the claim indefinite. The term "linker" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term “linker” is not defined in the Specification. The term linker can encompass functional groups, cyclic groups, linear and branched all of which can be substituted and replaced by

heteroatoms. Examiner has searched this term based upon the elected species which Q is CH2CH2 and definition of Q' has shown in claim 2.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "salts", does not reasonably provide enablement for "prodrugs". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention in the instant case has claims which embrace aryl piperidine compounds. The scope of "esters and prodrugs" is not adequately enabled. Applicants provide no guidance as how the compounds are made more active *in vivo*. The choice of a "esters and prodrugs" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which prodrugs will be suitable for the instant invention.

The instant compounds of formula (I) wherein the esters and prodrugs are not described in the disclosure in such a way the one of ordinary skill in the art would no how to prepare the various compounds suggested by said claims. In view of the lack of direction provided in the specification regarding starting materials, the lack of working

examples, and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention.

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for R being unsubstituted alkyl, benzofuran optionally substituted with Cl; R9 being H; Y being azepanyl, piperidinyl, pyranyl optionally substituted with OH; and X being cyclohexyl or phenyl unsubstituted, but does not reasonably provide enablement for R, R9, Y and X being the full scope as claimed along with all claimed substiutuents, for instant terms like “substituted”, “heteroaryl”, “fused aryl-heterocycloalkkyl”, “aryl" and “heterocyclic” and heterocyclic aryl”.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is “undue”; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Scope of the compounds. Owing to the range of many variables, millions of highly substituted N-phenyl-1H-indole-2-carboxamide compounds are embraced.

(2) The nature of the invention: The invention is a highly substituted N-phenyl-1H-indole-2-carboxamide compounds.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and chemical reactivity (which is affected by determinants such as substituent effects, steric effects, bonding, molecular geometry, etc) is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: That provided is very limited. Applicant shows a general synthesis of compounds of application's general formula I. The Specification describes starting materials and methods for synthesis of compounds wherein R being unsubstituted alkyl, benzofuran optionally substituted with Cl; R9 being H; Y being azepanyl, piperidinyl, pyranyl optionally substituted with OH; and X being cyclohexyl or phenyl unsubstituted, but does not describe or list any reagents wherein compounds can be used to synthesis compounds where R, R9, Y and X and substituents thereof as listed above. There is limited evidence in the Specification of the example compounds that only covers no or a small portion of the substituents claimed of formula. Thus,

there is no specific direction or guidance regarding said compounds specifically mentioned in Scope.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here…As per MPEP 2164.01 (b). A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to a make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court *in re Ghiron*, 442 F.2d 985, 991, 169 USPQ 723, 727 (CCPA 1971), made it clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

It is not trivial to experimentally interchange any and all of the many substituents that exist. As described by F. Zaragoza Dörwald, most organic syntheses fail initially and chemical research is highly inefficient due to chemists spending most of their time "finding out what went wrong and why". Therefore, most syntheses of organic compounds are labor-intensive and demanding. Additionally, most final synthetic routes to desired organic molecules are usually very different from initially planned routes. A

highly skilled chemist can agree that for many successful organic compounds made, many failures are encountered and experimental repetition is common. This also contributes to the burden and unpredictability of the syntheses of said compounds. (see "Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design" 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

(6) Working Examples: Applicant shows examples where R being unsubstituted alkyl, benzofuran optionally substituted with Cl; R9 being H; Y being azepanyl, piperidinyl, pyranyl optionally substituted with OH; and X being cyclohexyl or phenyl unsubstituted, but no working examples were shown wherein R, R9, Y and X and substituents thereof have been made or used of any kind.

(7) Skill of those in the art: The ordinary artisan is highly skilled, e.g. a masters or PhD level chemist.

(8) The quantity of experimentation needed: Since there are very limited working examples as described above, the amount of experimentation is expected to be high and burdensome.

Due to the level of unpredictability in the art, the very limited guidance provide, and the lack of working examples, the Applicant has not provided sufficient guidance for the artisan to make the invention.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the

evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while compounds being enabling for binding to CCR2 and CCR5 enzymes, does not reasonably provide enablement for treatment of an autoimmune or an inflammatory disease or condition AND treatment of HIV or AIDS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Pursuant to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see *In re Vaeck*, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims: Treatment or prevention of for treatment of an autoimmune or an

inflammatory disease or condition AND treatment of HIV or AIDS using compounds of Formula I.

(2) The nature of the invention: The invention is the method of using compounds of Formula I to treat an autoimmune or an inflammatory disease or condition AND treatment of HIV or AIDS.

(3) Level of predictability in the art: It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(4) Direction or Guidance: The Applicant does not show or demonstrate the use compounds and compositions of Formula I towards treatment or prevention of pain and inflammation. The Specification shows binding studies to CCR2 and CCR5 enzymes and describes the process. Additionally, the Applicant does not specifically disclose the exact compounds that were administered during these *in vitro* studies. However, there is very limited guidance or direction as how to treat an autoimmune or an inflammatory disease or condition AND treatment of HIV or AIDS using compounds of Formula I.

(5) State of the Prior Art: Treatment of autoimmune or an inflammatory diseases or conditions AND treatment of HIV or AIDS is not well developed and is highly

unpredictable. The state of the prior art for their treatments involve screening, *in vitro* and *in vivo,* that provides data to determine if compounds exhibit the desired analgesic and inflammatory activities. The Applicant has not provided any art recognized evidence that shows the use of compounds and compositions claimed for the prevention of pain and inflammation.

(6) Working Examples: The Applicant has provided no working examples to treat said diseases and conditions. Nor has Applicant directed the skilled artisan to disclosures in the art that may be used to extrapolate the intended use of the compounds and compositions for of autoimmune or an inflammatory diseases or conditions AND treatment of HIV or AIDS.

(7) Skill of those in the art: The ordinary artisan is highly skilled such as a medical doctor, doctor of philosophy in science, a nurse practitioner, etc.

(8) The quantity of experimentation needed: In the absence of working examples, which provide sufficient representative disclosures necessary to provide enablement for the treatment of autoimmune or an inflammatory diseases or conditions AND treatment of HIV or AIDS, undue experimentation would indeed be required to practice the instant invention. The amount of experimentation is expected to be unduly high and burdensome.

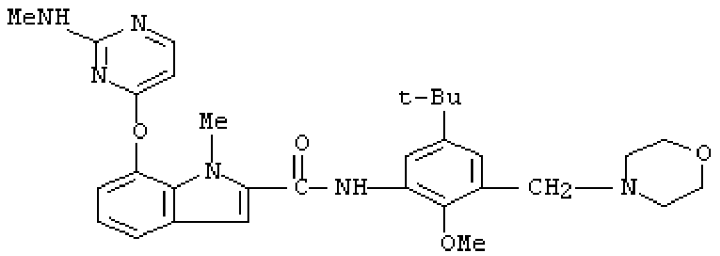
Claim Rejections - 35 USC § 102

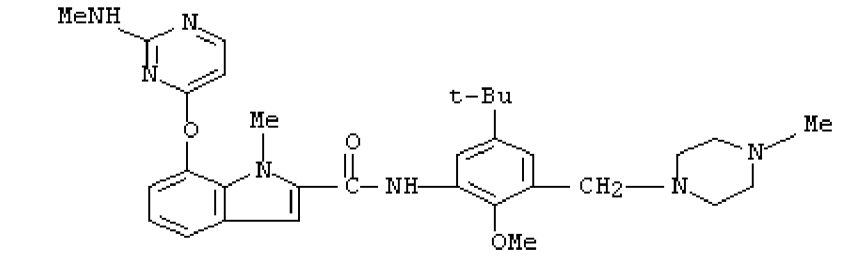
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

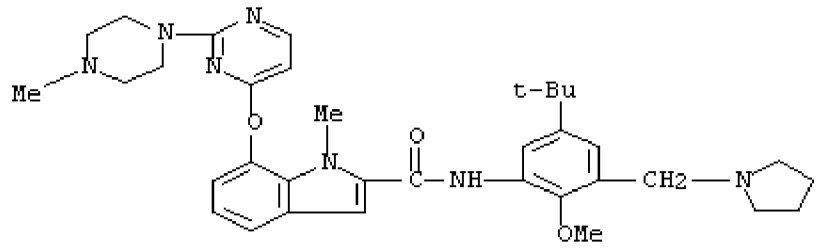
> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

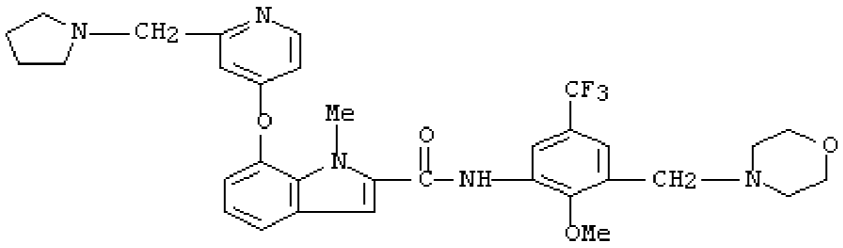
Claims 1, 2, 4, 5, 7 and 8 are rejected under 35 U.S.C. 102(e) as being anticipated by US 7,078,419.

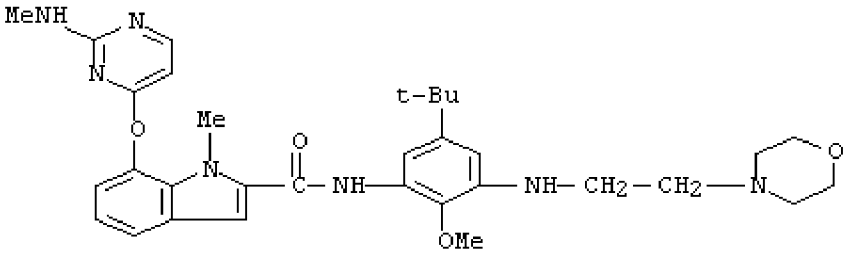
US ‘419 discloses compounds and pharmaceutical compositions of Formula I wherein Z=NR3 where R3 is methyl; R9=H; R=O-pyridinyl, O-1,3-pyrimidinyl; X=phenyl; Q=CH2, NHCH2CH2 and Y=morpholinyl, piperazinyl, pyrrolinyl (as shown below and bottom of columns 29/30; top of columns 31/32; middle of columns 33/34; and middle of columns 89/90). There are many more anticipated species within reference.











Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

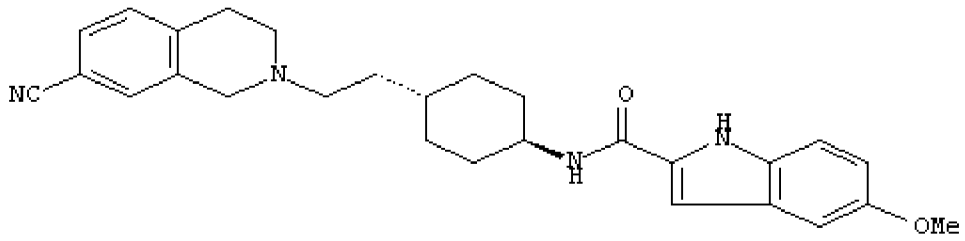
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 4, 5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,465,485 (PTO-1449).

The instant application claims compounds and pharmaceutical compositions of Formula I where Z=NR3 where R3 is methyl; R9=H; R=O-alkyl; X=phenyl; Q=CH2CH2 and Y=3,4-dihydroisoquinolinyl.

Scope & Content of Prior Art MPEP 2141.01

US '485 discloses compounds and pharmaceutical compositions of Formula I where Z=NR3 where R3 is H; R9=H; R=O-alkyl; X=cyclohexyl; Q=CH2CH2 and Y=3,4-dihydroisoquinolinyl (see Example 30, column 55).



Differences between Prior Art & the Claims MPEP 2141.02

US '485 differs from instantly claimed invention at the R position: US '485's –O-alkyl at the 6-position versus Applicant's –O-alkyl at the 4-position which are positional isomers. US '485 teaches that the 3,4-dihydroisoquinolinyl can be substituted with an alkoxy group at any position of the pheny ring (see column 4, lines 38-50).

Additionally, it is well established that position isomers are prima facie structurally obvious even in the absence of a teaching to modify. The isomer is expected to be prepared by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing the position isomers. This circumstance has arisen many times. See: *Ex parte Englehardt,* 208 USPQ 343, 349; *In re Mehta,* 146 USPQ 284, 287; *In re Surrey*, 138 USPQ 67; *Ex Parte Ullyot,* 103 USPQ 185; *In re Norris,* 84 USPQ 459; *Ex. Parte Naito,* 168 USPQ 437, 439; *Ex parte Allais,* 152 USPQ 66; *In re Wilder,* 166 USPQ 545, 548; *Ex parte Henkel,* 130 USPQ 474; *Ex parte Biel,* 124 USPQ 109; *In re Petrzilka,* 165 USPQ 327; *In re Crownse,* 150 USPQ 554; *In re Fouche,* 169 USPQ 431; *Ex parte Ruddy,* 121 USPQ 427; *In re Wiechert,* 152 USPQ 249, *In re Shetty,* 195 USPQ 753; *In re Jones,* 74 USPQ 152, 154. There may be others as well. Thus, said claims are rendered obvious by US '485 et al.

For example, "Position isomerism has been used as a tool to obtain new and useful drugs" (*Englehardt*) and "Position isomerism is fact of close structural similarity" (*Mehta*, emphasis in the original). Note also *In re Jones,* 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Position isomers are the basic form of close "structural isomers." Similar is *In re Schechter and LaForge,* 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also *In re Deuel* 34 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds…a known compound may suggest it analog or isomers, either geometric (cis v. trans) or position isomers (e.g. *ortho v. para*)." See also MPEP 2144.09, second paragraph. Further, the reference provides for the ring being substituted in any position.

Prima Facie Obviousness, Rational & Motivation MPEP 2142-2413

It would be obvious for an artisan of ordinary skill in the art to place the alkoxy group at any position about the phenyl ring in view of the teachings of US '485 and case law was cited above.

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in KSR noted that the analysis supporting a rejection under 35 U.S.C. 103 should

be made explicit. The Court quoting In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" KSR, 550 U.S. at___, 82 USPQ2d at 1396. Exemplary rationales that may support a conclusion of obviousness include:

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. See MPEP § 2143 for a discussion

of the rationales listed above along with examples illustrating how the cited rationales may be used to support a finding of obviousness. See also MPEP § 2144- §2144.09 for additional guidance regarding support for obviousness determinations.

The aforementioned reasons above describe rationales that support a conclusion of obviousness based upon the KSR International Co. *v.* Teleflex Inc. decision. Letters (A) - (E) rationale is supported above.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John Mabry, PhD whose telephone number is (571) 270-1967. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's primary examiner can be reached at (571) 272-0684, first, or the Examiner's supervisor, Janet Andres, PhD, can be reached at (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/John Mabry/
Examiner
Art Unit 1625

/Rita J. Desai/
Primary Examiner, Art Unit 1625